
A Sox9/Fgf feed-forward loop maintains pancreatic organ identity.

Journal: Development

Publication Year: 2012

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PubMed link: 22874919

Funding Grants: Interdisciplinary Stem Cell Training Program at UCSD II, Stem Cell Research Training Grant

Public Summary:

All mature pancreatic cell types arise from organ-specific multipotent progenitor cells. Although previous studies have identified cell-intrinsic and -extrinsic cues for progenitor cell expansion, it is unclear how these cues are integrated within the niche of the developing organ. Here, we present genetic evidence in mice that the transcription factor Sox9 forms the centerpiece of a gene regulatory network that is crucial for proper organ growth and maintenance of organ identity. We show that pancreatic progenitor-specific ablation of Sox9 during early pancreas development causes pancreas-to-liver cell fate conversion. Sox9 deficiency results in cell-autonomous loss of the fibroblast growth factor receptor (Fgfr) 2b, which is required for transducing mesenchymal Fgf10 signals. Likewise, Fgf10 is required to maintain expression of Sox9 and Fgfr2 in epithelial progenitors, showing that Sox9, Fgfr2 and Fgf10 form a feed-forward expression loop in the early pancreatic organ niche. Mirroring Sox9 deficiency, perturbation of Fgfr signaling in pancreatic explants or genetic inactivation of Fgf10 also result in hepatic cell fate conversion. Combined with previous findings that Fgfr2b or Fgf10 are necessary for pancreatic progenitor cell proliferation, our results demonstrate that organ fate commitment and progenitor cell expansion are coordinately controlled by the activity of a Sox9/Fgf10/Fgfr2b feed-forward loop in the pancreatic niche. This self-promoting Sox9/Fgf10/Fgfr2b loop may regulate cell identity and organ size in a broad spectrum of developmental and regenerative contexts.

Scientific Abstract:

All mature pancreatic cell types arise from organ-specific multipotent progenitor cells. Although previous studies have identified cell-intrinsic and -extrinsic cues for progenitor cell expansion, it is unclear how these cues are integrated within the niche of the developing organ. Here, we present genetic evidence in mice that the transcription factor Sox9 forms the centerpiece of a gene regulatory network that is crucial for proper organ growth and maintenance of organ identity. We show that pancreatic progenitor-specific ablation of Sox9 during early pancreas development causes pancreas-to-liver cell fate conversion. Sox9 deficiency results in cell-autonomous loss of the fibroblast growth factor receptor (Fgfr) 2b, which is required for transducing mesenchymal Fgf10 signals. Likewise, Fgf10 is required to maintain expression of Sox9 and Fgfr2 in epithelial progenitors, showing that Sox9, Fgfr2 and Fgf10 form a feed-forward expression loop in the early pancreatic organ niche. Mirroring Sox9 deficiency, perturbation of Fgfr signaling in pancreatic explants or genetic inactivation of Fgf10 also result in hepatic cell fate conversion. Combined with previous findings that Fgfr2b or Fgf10 are necessary for pancreatic progenitor cell proliferation, our results demonstrate that organ fate commitment and progenitor cell expansion are coordinately controlled by the activity of a Sox9/Fgf10/Fgfr2b feed-forward loop in the pancreatic niche. This self-promoting Sox9/Fgf10/Fgfr2b loop may regulate cell identity and organ size in a broad spectrum of developmental and regenerative contexts.

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